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A61K 38/12, A61P 33/02, 35/00, 37/00

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(88) Date of publication of the international search report:
20 July 2000 (20.07.00)

(54) Title: CYCLIC TETRAPEPTIDE AND THEIR USE AS HISTONE DEACETYLASE INHIBITOR

(57) Abstract

A cyclic tetrapeptide compound and use thereof. Especially, a compound WF27082, a process for production of the compound by culturing, in a nutrient medium, a WF27082-producing strain belonging to *Acremonium* and recovering the compound from a culture broth, a pharmaceutical composition containing the compound as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient, the compound for use as a medicament, a use of the compound for manufacture of a medicament for inhibiting histone deacetylase, a use of the compound for manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infections, organ transplant rejections, autoimmune diseases, or tumors, a use of histone deacetylase inhibitors as an immunosuppressant or an antitumor agent, and a use of histone deacetylase inhibitors for manufacture of a medicament for treating or preventing organ transplant rejections, autoimmune diseases or tumors are described.

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/JP 99/05597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/12 C12P21/04 C12R1/645 A61K38/12 A61P33/02
A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 11366 A (MERCK & CO INC ;DULSKI PAULA M (US); GURNETT ANNE M (US); MYERS RO) 27 March 1997 (1997-03-27) The whole document; see especially page 6 and claim 14 ---	1-20
A	GB 2 309 696 A (MERCK & CO INC) 6 August 1997 (1997-08-06) The whole document; see especially page 9 --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2000	16 05 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GROENENDIJK, M

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INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/JP 99/05597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199540 Derwent Publications Ltd., London, GB; Class B02, AN 1995-304271 XP002129775 & JP 07 196686 A (TAKEDA CHEM IND LTD), 1 August 1995 (1995-08-01) cited in the application abstract ---	
A	WO 97 35990 A (JAMISON TIMOTHY F ;HARVARD COLLEGE (US); TAUNTON JACK (US); HASSIG) 2 October 1997 (1997-10-02) the whole document -----	

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 99/05597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12,15,17,19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 4,9,10(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3,5-8,17,18 (complete); 4,9-16,19,20 (partially)

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 4,9,10(partially)

Present claims 4,9 and 10 relate to a compound or its preparation defined by reference to a desirable characteristic or property, namely a histone deacetylase inhibitory activity. The process of claim 9 is only described in terms of the compounds to be obtained and does not itself define said compounds.
These claims cover all compounds (and processes for their preparation) having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds (see claim 1). In the present case, said claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds and also the process for their preparation by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds defined in claim 1, their preparation and use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-3,5-8,17,18(all complete),4,9-16,19,
20(all partially)

Compounds as defined in claim 1, their preparation, their compositions and use and a strain as defined in claim 3,

2. Claims: 11-16,19,20(all partially)

Compositions as defined in claims 11 and 14 as far as relating to a compound according to the formula of claim 11 wherein R3 is hydrogen and R2 is methyl and their use

3. Claims: 19,20(all partially)

Use as defined in the claims 19 and 20 as far as not encompassed by the subjects 1 and 2

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Inter...al Application No
PCT/JP 99/05597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9711366 A	27-03-1997	AU 712801 B	18-11-1999
		AU 6979096 A	09-04-1997
		CA 2231251 A	27-03-1997
		EP 0855024 A	29-07-1998
		JP 11514857 T	21-12-1999
		US 5922837 A	13-07-1999
GB 2309696 A	06-08-1997	US 5922837 A	13-07-1999
JP 7196686 A	01-08-1995	NONE	
WO 9735990 A	02-10-1997	AU 2990597 A	17-10-1997